NTP
National Toxicology Program

Impact of Sex and Strain on the Performance of Genomic Signatures of Hepatocarcinogenesis

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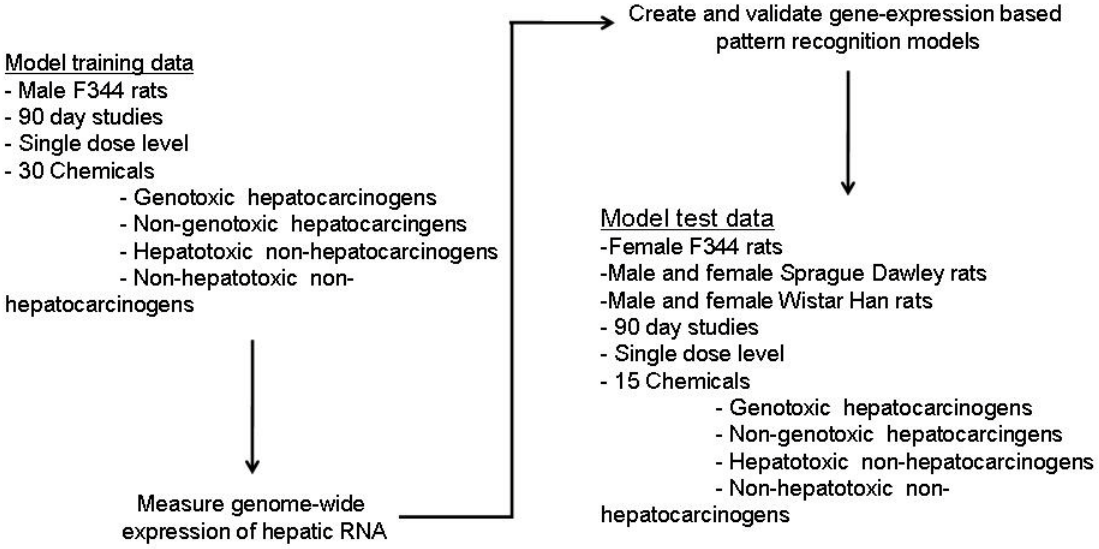
Background

- Functional genomic signatures (mRNA) can distinguish between hepatocarcinogens and non-hepatocarcinogens
- NTP* and others have developed these signatures
- Most signatures have been derived from and tested on gene expression from one strain of male rats or mice
- **Critical question: Do the signatures predict carcinogenic outcomes in other strains/sexes?**
  - Will be essential to answer before signatures can be confidently applied for hazard characterization

* Auerbach, S *et al.*, 2009.Predicting the Hepatocarcinogenic Potential of Alkenylbenzene Flavoring Agents Using Toxicogenomics and Machine Learning. *Accepted by Toxicology and Applied Pharmacology*

Proposed Approach



Key Issues

- Genetic diversity
  - Up to 50% of genetic loci (microsatellites) in F344, Sprague Dawley and Wistar Han rats are divergent
- Chemical selection
  - Broad mechanism of carcinogenic action
    - Particularly important for on-genotoxic hepatocarcinogens
  - Selection preference:
    - Chemicals studied in more than one strain of rat
    - Concordant carcinogenic response across species
- Dose selection
  - Approximate a high dose level from a 2-year study
  - Hepatocarcinogens: must produce at least 40% tumors by 2 years
  - Non-hepatocarcinogens: Concordance across strains / species
- Exposure duration (90 days)
  - Allows time to elicit robust genomic response at dose levels that would be selected for a 2-year study

Expected Outcomes

- Determine the degree to which genomic-based predictive models can be applied across strains/sexes
- Add to the growing database of genomic data that can be used for predictive modeling and cross-species extrapolation

Current Activities

- Chemical and dose selection